REMARKS

Claims 1-5, 7-8, 14-15, 22-24, 37, 39, and 61-75 are pending in this application. Claims 6, 9-13, 16-21, 25-26, 28-36, and 40-60 have been cancelled as being drawn to a nonelected invention. Claims 5 and 27 has also been cancelled. Claims 3, 4, 7, 8, 14, 15, 23, 24, 37, and 39 have been amended. New claims 61-76 have been added. The amendments to claims 3, 4, 8, 23, 37, and 39 are supported by the claims as originally filed. The amendment to claim 7 is supported by disclosure at page 18, lines 16-17 of the specification. The amendments to claims 14, 15, and 24 are supported by disclosure at page 4, lines 3-4 of the specification. New claim 61 is supported by disclosure at page 40, lines 1-9 of the specification. New claims 62, 67, 70, and 73 are supported by the claims as filed and by disclosure throughout the specification, *e.g.*, at page 12, lines 1-2. New claim 63 is supported by disclosure at page 12, lines 8-15 of the specification. New claims 64, 65, 68, 69, 71, 72, 74, and 75 are supported by disclosure at page 12, lines 14-19 of the specification. New claims 67-75 are further supported by disclosure at page 20, lines 23-27 of the specification. New claim 66 is supported by claim 1 as originally filed and by disclosure at page 29, lines 10-12 of the specification. New claim 76 is supported by disclosure at page 16, lines 4-24 of the specification. No new matter has been added.

REJECTION UNDER 35 U.S.C. §103

Claims 1-5, 7, 8, 14, 15, 22, 23, 27, 37, and 38 (misnumbered as 39 in the originally filed application) have been rejected under 35 U.S.C. §103(a) as obvious over Pettit *et al.*, WO99/35150 ("Pettit"), in view of Cahan *et al.*, Cancer Chemotherapy and Pharmacology, 33(5):441-4 (1994) ("Cahan"). Applicants traverse for the reasons discussed below.

It is well recognized under U.S. law, that any rejection of a claim for obviousness over a combination of prior art references must establish that: (1) the combination produces the claimed invention; and (2) the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention.[1] The motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention.[2] The mere fact that the prior art could be

[1] *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).
[2] *In re Napier*, 34 U.S.P.Q.2d 1782, 1784 (Fed. Cir. 1995).

modified does not make the modification obvious unless the prior art suggests the desirability of the modification.[3]

According to the Examiner, Pettit teaches the compound, Combretastatin A-4 Phosphate ("CA4P"), for the treatment of one or more neoplastic diseases, such as malignant melanoma, breast carcinoma, and ovarian carcinoma in humans. The Examiner also states that Cahan teaches that taxol has shown clinical activity against several tumors, including ovarian and breast carcinoma and melanoma. The Examiner concedes that Pettit and Cahan do not teach the combination together. However, the Examiner argues that "one skilled in this art would find ample motivation from the prior art supra to combine the well know [sic] anticancer agents together where the results obtained thereby are no more than the additive effects of the anticancer agents; particularly since the above prior art teaches the ingredient for treating the same cancer systems." Office Action dated 07/03/03 at page 3.

Applicants submit that it would not have been obvious to one of ordinary skill in the art to have used CA4P and its analogs in combination with taxanes and its analogs as CA4P has a completely different mode of action from taxanes. Accordingly, Applicants submit that the prior art does not contain a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention.

The taxanes are a group of drugs, including paclitaxel and docetaxel, which are used in the treatment of cancer. Taxanes inhibit cancer cell growth by stopping cell division, and are called antimitotic or antimicrotubule agents or mitotic inhibitors. As defined in the specification, a mitotic inhibitor is a compound that can inhibit mitosis needed for reproduction of the cell and includes taxanes such as paclitaxel and docetaxel. *See Specification* at p. 14, lines 1-9. Taxanes represent a class of antineoplastic agents that act by shifting the dynamic equilibrium between tubulin and microtubules in the direction of microtubule assembly. The cells become blocked during the G2 and M cell cycle phases and cannot form a normal mitotic spindle and divide. Essentially, these microtubules are excessively stable and therefore dysfunctional. In normal cell growth, microtubules are formed when a cell starts dividing. Once the cell stops dividing, the microtubules are broken down or destroyed. Taxanes stop the microtubules from breaking down; cancer cells become so clogged with microtubules that they cannot grow and divide.

[3] *In re Laskowski*, 10 U.S.P.Q.2d 1397, 1399 (Fed. Cir. 1989).

Taxanes are thus known by skilled artisans to enhance microtubulin assembly. In contrast, combretastatins are known by skilled artisans to be potent inhibitors of microtubulin assembly. *See Specification* at p. 3, lines 23-27, and p. 24, lines 1-5. In addition to inhibiting microtubulin assembly, CA4P has also been shown to be a vascular targeting agent. This mechanism of action is to attack the vasculature within the tumor itself, reducing blood flow to deprive the tumor of oxygen and nutrients, causing tumor cell death. Combretastatin A4 Prodrug starves existing solid tumors by depriving them of the blood flow that feeds the tumor, causing tumor cell death. Combretastatins, therefore, are inhibitors of tubulin assembly which also are vascular targeting agents. They are not tubulin polymerizers.

As disclosed in the specification, and known by those skilled in the art, CA4P and taxanes have opposite modes of action. The mechanism of action of CA4P is to depolymerize tubulin while that of paclitaxel is to polymerize tubulin. *See Specification* at p. 39, lines 19-20. Accordingly, one skilled in the art would be likely to reason that the anticancer action of these compounds would be negated if used in combination. Thus, one skilled in the art would not reasonably expect a combretastatin compound to be successfully combined with a taxane as a therapeutic for cancer. Therefore, Applicants submit that one of ordinary skill in the art would not be motivated to combine the teachings of Pettit regarding combretastatin compounds and those of Cahan regarding taxol to obtain the combination therapy because of their opposing mechanisms of action.

Indeed, the specification teaches that administration of CA4P and paclitaxel simultaneously can be deleterious to the overall efficacy of the combination. *See Specification* at p. 40, lines 2-5 and Figure 9. Further guidance was necessary to determine an efficacious treatment schedule. As disclosed in the present application, allowing an interval of 24 hours between administration of the agents where paclitaxel is administered prior to CA4P or an interval of 3 hours between administration of the agents where CA4P is administered prior to paclitaxel, resulted in an efficacious combination treatment schedule. *See Specification* at p. 40, lines 2-14. Therefore, Applicants assert that the methods and compositions of the pending claims, as amended herein, are not obvious to one skilled in the art. Applicants request reconsideration and withdrawal of this rejection.

CONCLUSION

In view of the aforementioned remarks and amendments, the Applicants believe that each of pending claims is in condition for allowance. Reconsideration, withdrawal of the rejections, and passage of the case to issue is respectfully requested. A notice to this effect is earnestly solicited.

If, upon receipt and review of this amendment, the Examiner believes that the present application is not in condition for allowance and that changes can be suggested which would place the claims in allowable form, the Examiner is respectfully requested to call Applicant's undersigned counsel at the number provided below.

Respectfully submitted,

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